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Shedding light on allogeneic hematopoietic stem cell transplantation success: exploring the relationship between donor vitamin D and parathormone levels and recipient engraftment and stem cell quantity

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ABSTRACT

Aims: The aim of this study is to investigate whether pre-mobilization serum vitamin D and parathormone levels in allogeneic hematopoietic stem cell transplantation (allo-HCT) donors have an impact on the collected stem cell quantity and engraftment periods in recipients.

Methods: Data from 35 donors aged 18 and over, who served as donors in allo-HCT performed between 2019 and 2021 at Erciyes University Faculty of Medicine, Bone Marrow Transplantation and Stem Cell Treatment Center, were retrospectively analyzed. Donors with known pathologies related to the parathyroid gland, unrelated and bone marrow-derived stem cell donors were excluded from the study. Donors were grouped as low and high based on serum vitamin D and parathormone levels. The possible relationship between these values and total product CD34+ cell count, neutrophil engraftment time, and platelet engraftment time was assessed.

Results: It was found that recipients of donors with high vitamin D levels had significantly earlier platelet engraftment days compared to donors with low vitamin D levels (p=0.026). In donors with high vitamin D levels, it was observed that the peripheral CD34+ cell count was lower, and the total product CD34+ cell count was higher, although there was no significant relationship (p>0.05). Although recipients of donors with high vitamin D levels had earlier neutrophil engraftment times, no significant relationship was found (p=0.29). A moderate negative correlation was found between platelet engraftment times and vitamin D levels. There was no statistically significant relationship between parathormone levels and stem cell quantities and engraftment times.

Conclusion: Vitamin D deficiency in allo-HCT donors before mobilization was observed to prolong platelet engraftment times in recipients. Therefore, we recommend correcting vitamin D levels in donors before allo-HCT.

Keywords: Allogeneic hematopoietic stem cell transplantation, engraftment, parathormone, vitamin D

INTRODUCTION

Vitamin D plays a role not only in bone and mineral metabolism but also in various physiological events.[1] Active vitamin D exhibits its biological functions by binding to the vitamin D receptor (VDR). The discovery that most tissues and cells in the body possess VDR has led to extensive research on the potential effects of vitamin D on the hematopoietic and immune systems.[2-5] In the hematopoietic system, the presence of VDR has been identified in hematopoietic precursor cells, monocytes, activated B and T lymphocytes, and thymocytes.[3,5] In a study conducted on mice, it was observed that administration of active vitamin D to mice with VDR led to differentiation and maturation towards monocytes/macrophages in hematopoietic stem cells (HSCs); however, this effect was not observed in mice without VDR.[6,7] The presence of VDR on activated lymphocytes and natural killer cells suggests its role in differentiated cells.[8,9] Due to its immunoregulatory effects, many studies have evaluated the impact of vitamin D in patients undergoing allogeneic hematopoietic stem cell transplantation (allo-HCT).[10-13]

Parathyroid hormone (PTH) is another hormone shown to play a role in regulating the microenvironment of HSCs and has particularly positive effects on HSC mobilization. This

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effect is believed to contribute to positive outcomes post-transplantation. In many studies, PTH has been shown to activate osteoblasts that secrete hematopoietic growth factors, thereby increasing the number of HSCs.[14]

In allo-HCT, the resolution of neutropenia and thrombocytopenia in recipients after the conditioning regimen is achieved through the reconstitution of cell lineages following stem cell infusion. Engraftment development is crucial for overall survival after stem cell transplantation.[15] The peripheral blood CD34+ cell count measured after mobilization and before the apheresis procedure is one of the most important predictors used to estimate the quantity of CD34+ cells in the product. Alongside the challenges in treating hematological diseases, inadequate stem cell collection from donors and delayed engraftment in patients can increase mortality.[16] By preventing vitamin D and PTH deficiency through measures taken during the transplant process and the administration of appropriate treatment, significant reductions in the incidence of potential complications can be achieved. Therefore, we aimed to examine the relationship between 25(OH) vitamin D and PTH levels with engraftment periods and CD34+ stem cell quantities.

METHODS

Ethics

The study was evaluated by the Ethics Committee of Erciyes University Faculty of Medicine (Date: 22.07.2020 Decision No: 2020/388). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Data from individuals who served as donors and recipients in allogeneic hematopoietic stem cell transplantation (allo-HSCT) at Erciyes University Faculty of Medicine, Bone Marrow Transplantation, and Stem Cell Treatment Center between October 2019 and March 2021 were retrospectively examined, both from written and electronic records. The study included a total of 35 adult stem cell donors aged between 18 and 65 who had undergone hematopoietic stem cell mobilization. Only peripheral stem cell donors were included, and unrelated stem cell donors were excluded.

Data such as age, sex, height, weight, peripheral blood CD34+ cell count, total product CD34+ cell count, administered granulocyte colony-stimulating factor (G-CSF) dose, duration of G-CSF administration, number of apheresis procedures, total product volume, total plasma volume, product viability (%), neutrophil engraftment time, and platelet engraftment time were obtained from medical records of allo-HSCT donors and recipients.

Evaluation of serum 25(OH) vitamin D level, PTH, and other biochemical data from donors was conducted before stem cell mobilization. Serum 25(OH) vitamin D levels were measured using the electrochemiluminescence immunoassay method with the cobas 8000 Roche device at Erciyes University Faculty of Medicine Biochemistry Laboratory.

Stem Cell Mobilization and Apheresis

As a mobilization regimen, G-CSF was subcutaneously administered to hematopoietic stem cell donors at a dose of 10 mcg/kg/day for a minimum of 4 days. Generally, on the 5th day of G-CSF administration, the CD34+ cell count in peripheral blood was evaluated using flow cytometry. Depending on the responsible physician's patient and donor-based decision, the threshold value could vary, but generally, donors with a peripheral blood CD34+ cell count >10/mcl underwent apheresis. For donors who did not reach the target CD34+ cell count, G-CSF administration was continued. Apheresis procedures were continued until the target total product CD34+ cell count was achieved, with a lower limit accepted as 2x10^6/kg CD34+ cell count.

The Optia Apheresis System device was used for apheresis procedures. Typically, when a sufficient number of CD34+ cells were obtained in peripheral blood on the 5th day of G-CSF administration, apheresis was performed to collect stem cells from donors. During the procedures, an average of 2-3 times the donors' blood volume was processed. Acid citrate dextrose solution A (ACD-A) was given to donors as an anticoagulant during the procedure, and calcium replacement was performed to prevent hypocalcemia.

Statistical Analysis

SPSS 25.0 statistical software was used for data analysis. Descriptive statistics, including counts, percentages, means, standard deviations, medians, minimum, and maximum values, were utilized. Before proceeding to analytical tests, the distribution of the data was examined using the Shapiro-Wilk test. The Mann-Whitney U test was employed for the analysis of independent quantitative variables with non-normal distribution. Spearman correlation analysis was used for the correlation analysis of non-normally distributed quantitative variables. P values less than 0.05 were considered statistically significant in all analyses.

RESULTS

There were a total of 35 allo-HCT donors, including 11 (31.4%) women and 24 (68.6%) men. The mean age in the study group was 39.4±13.8 years. All donors received at least 4 days of G-CSF, and apheresis procedures commenced after the fourth day. The mean duration of G-CSF administration was 4.9±0.36 days. A single apheresis session was applied to 97.1% of the donors, while only one donor (2.9%) received two sessions of apheresis.

The mean peripheral blood CD34+ cell count, evaluated generally on the 5th day of G-CSF administration, was 101.4±51.1/mcl, and the mean total product CD34+ cell count was 6.7±1.3x10^6/kg (Table 1). The mean neutrophil engraftment day in recipients post-transplantation was 17±4.1 days, while the mean platelet engraftment day was 14.5±5.4 days.

Tablo 1. Apheresis outcomes for donors and engraftment days for patients

	Mean	SD
Peripheral blood CD34+ cell count (/mcl)	101.4	51.1
Total product CD34+ cell count (x106/kg)	6.7	1.3
Administered G-CSF dose (mcg)	80.1	13.8
Total product volume (ml)	244.1	146.7
Product viability rate (%)	98.8	2.7
Neutrophil engraftment day	17.0	4.1
Platelet engraftment day	14.5	5.4

SD: Standard deviation, G-CSF: Granulocyte colony-stimulating factor

The mean 25(OH) vitamin D level in donors was 18.7±8 ng/ml, and the PTH level was 34.8±18.3 pg/ml. The mean B12 vitamin level was 336.4±90.2 pg/ml, and folate levels were 8.2±2.5 ng/ml.

Evaluation of Donors' 25(OH) Vitamin D Levels and Clinical Characteristics

Donors with 25(OH) vitamin D levels below 20 ng/ml were considered low, while those with 20 ng/ml and above were considered high. It was observed that 54.3% of the donors had low levels of vitamin D. The comparison of donors' clinical characteristics based on vitamin D levels is presented in **Table 2**. It was found that recipients of donors with high vitamin D levels had significantly shorter platelet engraftment times compared to donors with low vitamin D levels (p=0.026). Although donors with high vitamin D levels had a lower peripheral blood CD34+ cell count and a higher total product CD34+ cell count, there was no statistically significant relationship (p>0.05). While the neutrophil engraftment times in recipients of donors with high vitamin D levels were shorter, it was not statistically significant (p=0.29). A moderate negative correlation was found between platelet engraftment times and vitamin D levels (r: -0.36, p: 0.03).

Tablo 2. Comparison of vitamin D levels with clinical characteristics

	Low vitamin D (n=19) (mean±SD)	High vitamin D (n=16) (mean±SD)	p*
Peripheral blood CD34+ cell count (/mcl)	104.7±57.4	97.6±44.1	0.756
Total product CD34+ cell count (x10^6/kg)	6.5±1.4	7.0±1.2	0.935
Total product volume (ml)	227.6±159.5	263.7±132.3	0.317
Product viability rate (%)	99.1±2.0	98.5±3.3	0.961
Neutrophil engraftment day	18.0±4.6	15.8±3.3	0.286
Platelet engraftment day	16.4±6.0	12.3±3.5	**0.026**

*Mann-Whitney U test was used, SD: Standard deviation

Evaluation of Donors' PTH Levels and Clinical Characteristics

In donors, parathormone levels below 15 pg/ml were considered low, while those at 15 pg/ml and above were considered high. It was observed that 14.7% of donors had low parathormone levels. In donors with high PTH levels, it was found that peripheral blood CD34+ and total product CD34+ cell counts were lower, but there was no statistically significant relationship between them (p>0.05). Additionally, it was observed that recipients of donors with high PTH levels had shorter neutrophil and platelet engraftment times, but there was no statistically significant relationship (p>0.05) (**Table 3**).

Tablo 3. Comparison of donors' PTH levels with clinical characteristics

	Low PTH (n=5) (mean±SD)	High PTH (n=30) (mean±SD)	p*
Peripheral blood CD34+ cell count (/mcl)	118.6±55.4	98.6±50.8	0.506
Total product CD34+ cell count (x10^6/kg)	7.4±0.9	6.6±1.3	0.299
Total product volume (ml)	236.0±91.5	245.5±155.1	0.873
Product viability rate (%)	99.5±0.2	98.7±2.9	0.945
Neutrophil engraftment day	18.6±3.5	16.7±4.2	0.237
Platelet engraftment day	15.0±3.2	14.4±5.7	0.395

*Mann-Whitney U test was used, SD: Standard deviation, PTH: Parathyroid hormone

DISCUSSION

Allo-HCT remains an effective treatment option for many diseases, providing a chance for complete recovery. Successful allo-HCT requires an adequate infusion of HSCs in the recipient after the preparative regimen to allow hematopoietic reconstitution. Inadequate HSC infusion can negatively impact post-transplant hematopoietic reconstitution, leading to engraftment delays and graft failure, which may increase the risks of infection, bleeding, and transplant-related mortality. Mobilization failure is still a significant problem in the allo-HCT process, with reported rates ranging from 5% to 40%.[17] The generally accepted view is that the total product CD34+ cell count should reach a minimum threshold of 2x10^6/kg for successful transplantation to proceed.[18,19] However, Stiff et al.[20] suggest aiming for total product CD34+ cell counts above 4-5x10^6/kg to achieve positive effects such as faster neutrophil and platelet engraftment, shorter hospitalization periods. In our study, the median total product CD34+ cell count for all donors was 6.7x10^6/kg, surpassing the minimum threshold of 2x10^6/kg. The observed mobilization failure rate in our study appears to be lower compared to other studies.

Mikirova et al.[21] demonstrated an increase in peripheral blood CD34+ cell count in healthy adult volunteers after two weeks of receiving a dietary product containing lactobacillus, beta 1,3-glucan, ellagic acid, and vitamin D (Stem-Kine). However, since vitamin D was not administered alone in this study, evaluating the possible isolated effect of vitamin D is not feasible. In a study by Grande et al.[22] the addition of supraphysiological doses of vitamin D to the environment induced differentiation of HSCs toward monocytes/macrophages, resulting in a decrease in CD34+ CD38- cell count. Although higher levels of vitamin D were associated with a lower peripheral blood CD34+ cell count and a higher total product CD34+ cell count, this relationship was not statistically significant. In our study, we found no significant correlation between pre-mobilization 25(OH) vitamin D levels and peripheral blood or total product CD34+ cell counts in donors.

Hansson et al.[23] found that PTH positively influenced the HSC pool by stimulating the NOTCH signaling pathway. In a study by Brunner et al.[24] the effects of PTH and G-CSF on HSC mobilization in mice were compared. Similar to G-CSF, the administration of PTH increased the peripheral blood HSC count by 1.5-9.8 times. When endogenous G-CSF was targeted with antibodies, the positive effect of PTH on mobilization diminished. Therefore, it was suggested that PTH supports HSC mobilization through the release of endogenous G-CSF. In another study by Brunner et al.[25]on humans, a significant increase in circulating HSCs was found in individuals with primary hyperparathyroidism. In a study by Ballen et al.[26] patients with previous mobilization failure in autologous HSC transplantation were given PTH and G-CSF, and it was reported that the combined use of PTH and G-CSF met mobilization criteria in 45% of patients. The median neutrophil engraftment day was 11 (8-12) days, and the median platelet engraftment day was 19 (12-36) days, similar to reported engraftment times in the literature. With these data in mind, it is speculated that PTH administration, clinically approved for osteoporosis

treatment, could be a new treatment option in stem cell transplantation. In our study, we found no significant correlation between serum PTH levels measured in donors before allo-HCT mobilization and total product CD34+ cell count, neutrophil engraftment day, and platelet engraftment day.

Limitations

The main limitation of our study is its retrospective nature and the small number of donors involved. Another limitation is that it is a single-center experience, making the results less generalizable. Given the prevalence of vitamin D deficiency, its affordable and reliable treatment, further research is needed to investigate the potential effects of vitamin D in stem cell transplantation.

CONCLUSION

In allo-HSCT, high serum 25(OH) vitamin D levels in pre-mobilization donors were observed to shorten the platelet engraftment time in recipients. However, no significant correlation was observed between stem cell quantity and neutrophil engraftment time and donor 25(OH) vitamin D levels. There was no statistically significant correlation between PTH levels and engraftment times and stem cell quantities. Given the results of our study and the data in the literature, it has been concluded that the serum levels of vitamin D and PTH observed in allo-HCT pre-mobilization donors require more comprehensive and multi-centric advanced studies to shed light on the possible effects in the allo- HCT process and be incorporated into clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was a prospective cross-sectional study and the protocol of the study was approved by the Erciyes University Clinical Researches Ethics Committee (Date: 22.07.2020, Decision No: 2020/388).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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